

Summary of Safety and Effectiveness

I. GENERAL INFORMATION

Device Generic Name: Total Hip System, Ceramic Articulation

Device Trade Name: Reflection® Ceramic Acetabular System

Applicant's Name and Address: Smith & Nephew, Inc.
Orthopaedic Division
1450 Brooks Road
Memphis, Tennessee 38116

Premarket Approval (PMA) Number: P030022

Date of Panel Recommendation: None

Date of Notice of Approval to the Applicant: DEC 17 2004

I. INDICATIONS FOR USE

The Reflection® Ceramic Acetabular System is indicated for use in patients requiring primary total hip arthroplasty due to non-inflammatory arthritis (degenerative joint disease) such as osteoarthritis, avascular necrosis, or traumatic arthritis.

II. CONTRAINDICATIONS

The Reflection® Ceramic Acetabular System is contraindicated in individuals exhibiting any of the following:

- Insufficient quantity or quality of bone support; metabolic bone disease; osteoporosis
- Neurological or muscular conditions that would place extreme load or instability upon the hip joint;
- Active joint infections or chronic systemic infection
- Obese patients where obesity is defined as three times normal body weight
- Skeletal immaturity

III. WARNINGS and PRECAUTIONS

The warning and precautions can be found in the Reflection® Ceramic Acetabular System's physician's labeling.

IV. DEVICE DESCRIPTION

The Reflection® Ceramic Acetabular System consists of a ceramic on ceramic acetabular bearing couple combined with a compatible metal shell and one of two commercially available Smith & Nephew femoral stems described below. All implantable devices are supplied sterile (see sterilization section) and are for single use.

The bearing surfaces consist of Alumina Ceramic Heads (28mm and 32mm sizes in three neck lengths i.e. short, medium and long) and Alumina Ceramic acetabular Liners/inserts (internal diameters of 28mm and 32mm). The ceramic femoral heads have been previously cleared for use with polyethylene acetabular inserts in K981847 and K991162. Both components are manufactured of BioloX® forte Aluminum Oxide (ISO 6474 and ASTM F603) manufactured by CeramTec.

The ceramic femoral heads of the Reflection® Ceramic Acetabular System are intended to be used in conjunction with Smith & Nephew's commercially available titanium alloy (ASTM F1472), cementless Synergy femoral stems or cobalt chromium alloy (ASTM F799), cemented Spectron EF stems, both available in standard and high offset versions. The Synergy stems have a sintered, beaded porous coating made from commercially pure titanium (ASTM F67) on the proximal surface. The Spectron EF stems are collared and have a nonporous, grit blasted proximal surface. The Synergy and Spectron EF femoral stems both have a 131° neck angle and have been previously cleared for use in K963509 and K970351, respectively.

The ceramic acetabular inserts of the Reflection® Ceramic Acetabular System are intended to be used in conjunction with Smith & Nephew's hemispherical, Reflection FSO 5 shells for cementless use. The shell's internal geometry has a Morse taper that locks the ceramic liner when inserted. The titanium alloy acetabular shells have a sintered, beaded porous commercially pure titanium coating (ASTM F67) on the surface. The acetabular shells have an apex hole to accept the cup positioner/impactor instrument and five additional holes arranged about the apex hole for adjunctive screw fixation to the superior acetabulum if desired. The acetabular shells are to be implanted with optional Universal Cancellous Bone Screws (manufactured by Smith & Nephew). The acetabular shells are available in 11 sizes ranging from 46 to 66 mm outer diameters in 2 mm increments.

V. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative procedures include the election not to have surgery and use a more conservative treatment consisting of reduced activity and/or pain medication, hip fusion or hip joint replacement surgery with another commercially available total hip prosthesis. Commonly used implant materials for total hip arthroplasty include metallic prostheses using articulating bearing surfaces made of a combination of metallic and ultra-high molecular weight polyethylene (UHMWPE), ceramic and

UHMWPE, metal/metal, or ceramic on ceramic bearing articulations. Total hip prostheses are implanted by either cemented or uncemented techniques.

VI. MARKETING HISTORY

The Reflection® Ceramic Acetabular System has been marketed internationally in the European Union since October, 1998, in Australia since February, 1999, and in Canada since April, 2002. The Reflection® Ceramic Acetabular System has not been withdrawn from any country due to safety and effectiveness reasons.

Adverse events reported by international use are similar to those seen in this study and include chipped ceramic liners, liner fractures, shell deformation, ceramic head fracture, hip squeak, package malfunction, osteolysis.

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential Complications Associated with Any Total Hip Arthroplasty surgery

- excessive wear of the implant components secondary to impingement of components or damage of articular surfaces
- fracture, migration, loosening, subluxation, or dislocation of the prosthesis or any of its components; any of which may require a second surgical intervention or revision
- intractable pain
- unintended bone fractures
- metal sensitivity reactions or other allergic/histological reactions to implant material
- vascular damage resulting in large blood loss, or
- neurologic injury resulting in transient or permanent functional and/or sensory deficits
- leg length change/discrepancy
- deep venous thrombosis
- pulmonary or vascular embolism
- superficial or deep infection, delayed wound healing
- periarticular calcification
- myocardial infarction
- Gastrointestinal complications
- Genitourinary complications
- Decreased range of motion
- Aggravation of other joint or back conditions (due to positioning during surgery, postoperative leg length discrepancy, muscular deficiencies, etc.)
- death

Potential Complications Associated with Ceramic on Ceramic Hip Systems

Due to the materials of the device, these may include, but are not limited to, femoral head breakage, acetabular insert (liner) fracture, component dissociation dislocation and component wear debris. Other adverse events, common to other hip systems may also occur but at different frequencies.

VIII. SUMMARY OF PRECLINICAL STUDIES

A battery of pre-clinical tests was conducted on the alumina ceramic material used to make the ceramic components. Several nonclinical laboratory studies were conducted in support of the Reflection® Ceramic Acetabular System.

1. Biocompatibility

Extensive biocompatibility testing has been performed on bulk and powdered alumina. The alumina material conforms to the ASTM F603 and ISO 6474 requirements and has proven to be safe and effective. Femoral heads manufactured from this material have been in commercial distribution in the U.S. for over 15 years with no reported biocompatibility issues.

2. Acetabular Insert Rotational Stability, Lever-Out, and Push-Out Strength

The purpose of these tests was to evaluate the integrity of the insert/shell connection i.e. locking mechanism of the acetabular system. For torsional testing (rotational stability) seven of the smallest inserts (28/37G) were tested as this represents the worst case (i.e., least contact area). The average rotational moment (torque) of the acetabular construct was 1572.6 Ncm (normalized to 4250 N/m). Normalization was performed to account for differences in diameters of the metal/UHMWPE constructs to which the Reflection constructs were compared. The normalized torque for the Reflection was greater than all but two of the eight metal/UHMWPE constructs evaluated for comparison.

Three inserts were used for lever-out testing. The lever-out moment for the alumina insert was 106.34 Nm. Failure occurred in the lever arm, while the insert remained intact. The alumina insert performed superior to all eight metal/PE combinations that were evaluated, which had lever-out moments ranging from 11.3 to 99.5 Nm.

For the push-out test, a total of five of the smallest ceramic inserts (28/37G) were evaluated. This represents the thinnest insert available in the 28mm diameter size, which is the worst case with respect to push-out resistance. The mean push-out force was 1131 N, with no failures below 1000 N.

The integrity of the ceramic insert/shell connection (i.e. locking mechanism) of the acetabular system as tested in the torsion, push-out and lever-out testing demonstrates that the ceramic/metal shell construct locking mechanism is comparable to those of commercially available UHMWPE/metal shell constructs, and therefore, should perform as intended under expected in vivo loading conditions.

3. Wear of Ceramic Head / Ceramic Insert to 10 Million Cycles

Cyclic fatigue testing was performed to evaluate the generation of ceramic wear out to 10 million cycles. A total of six ceramic head/cup (smallest head/insert) pairs were tested at a rate of 2 Hz. Specific loading and other test conditions resulted from extensive research to identify the most clinically relevant test methodology. A 100% Hyclone modified bovine serum was used as lubricant and replaced at weekly intervals. Serum concentration/protein content was 100% and 40-44 g/l, respectively. Surface roughness was measured pre- and post-testing for comparison via interferometry. Weight measurements of shells, inserts, and heads were also taken at these intervals. Finally, compressive burst tests were performed on three heads at the end of the wear testing for comparison to new ceramic heads.

Results demonstrated that surface roughness of the femoral head and outer surface of the insert increased, while there was no change in the roughness of the inner articulating surface of the insert. This test demonstrated that there was no appreciable generation of ceramic wear debris compared to typical wear rates/volumes for other clinically successful bearing materials.

Burst testing also indicated there was no significant reduction in the axial compressive strength for femoral heads that had undergone wear testing. The mean burst strength for wear tested heads was 52.5 kN, and the mean burst strength for heads not subjected to wear testing was 55.7 kN. All devices fractured at loads greater than 20 kN (as suggested in the FDA Ceramic Ball guidance). Therefore, this wear testing/post-wear burst testing appears to have sufficient strength and durability to perform under expected loading conditions

4. SEM/EDXA of Post-Wear Testing Debris and Components

Wear-tested samples were further evaluated by SEM and EDXA (energy dispersive x-ray analysis) to assess surface changes of the components that might be indicative of wear. In addition, a nitric acid digestion was performed on the wear debris from two samples to eliminate bovine serum and permit SEM/EDXA analysis of the remaining particulate. Wear tested components were examined at low and high magnification and compared to control specimens that had not undergone testing. Both test and control components showed similar features including machine lines at 5000X magnification. EDXA analysis of the particles on the surface of the head showed no identifiable elements. The particles were believed to be deposits of protein from bovine serum. The test specimen did show minor pits and small areas of abrasions, but no other significant differences compared to the control specimen. The acetabular inserts showed similar lines including pitting and machine lines. Two particles of titanium were discovered embedded in a scratch on the articular surface of the insert. The particles were 15.4 and 29.5 microns in length.

The wear debris was filtered through a 0.05 micron polycarbonate membrane after nitric acid digestion. Two samples were examined at a magnification of 10,000X to permit counting and analysis of residual particles in ten fields of view. EDXA analysis showed that none of the small particles (less than 1 micron) were ceramic. Larger ceramic particles were identified but were few in number.

This test demonstrated that there was no appreciable generation of ceramic wear debris compared to typical wear rates/volumes of other clinically successful bearing materials.

5. Ceramic Head Static Axial Compression Test (Burst Strength)

Burst or 'crush' testing was performed to evaluate the ability of the individual ceramic components and the system as a whole to withstand static axial compression. In addition, burst testing of the femoral head was performed according to standard methods and an alternative worst case point loading method.

Testing of the ceramic heads was performed using five 28mm medium (+4) alumina ceramic heads (worst case) mounted on 12/14 taper CoCr trunnions per ISO 7206-5 and the FDA Ceramic Ball guidance document. The results showed that the average load to fracture the heads was 50.5 kN, with no head fracturing below 45.6 kN. All failures were characterized by sudden catastrophic brittle fracture with fragmentation of the head into small pieces. These failure values exceed the minimum requirements of average burst strength of 46 kN and no individual failure below 20 kN, as suggested in the Ceramic Ball guidance document.

Static compression burst testing was again performed according to ISO 7206 using the longest neck extension (+8, which is worse case) on 12/14 taper Ti6Al4V alloy trunnions. Five heads were tested. The average compressive burst strength of all of the alumina/Ti6Al4V hip stem trunnion pairs exceeded the 46 kN average minimum identified in Ceramic Ball guidance. Average fracture load was 55.7 kN and no head failed at less than 50 kN.

A second type of burst test was conducted to evaluate head burst strength under point loading conditions. For the current submission, six 28mm alumina heads (+8) were mounted on 12/14 CoCr trunnions. An axial compressive load was applied at 2.54 mm/min until the head fractured. The average compressive load when tested in this way was approximately 32.7 kN, with no individual specimen failing below 30.3 kN. These 28mm long (+8) alumina femoral heads for use on CoCr stems were cleared with this testing in K991162, then added to this clinical study.

These results indicate the ceramic heads possess sufficient strength to perform as intended under expected *in vivo* loading conditions.

6. Ceramic Inserts Static Axial Compression Test (Burst Strength)

Alumina inserts were burst tested using systems comprised of the alumina ceramic inserts and zirconia ceramic heads. Seven 28/37G inserts were inserted into 50mm metal shells by applying a 2 kN load. It is noted that for the seven inserts tested here the average value was just slightly less (45.6kN) than that 46 kN 'requirement.' This may be due to the high safety factor of this value in comparison to maximum expected *in-vivo* loads during gait (5.5X's body weight, so for a 165 lb man a maximum load of only 4 kN). In addition, see post-fatigue residual burst testing results in section below (those results are higher than 46 kN).

The ceramic insert testing demonstrates that the inserts possess adequate strength to perform as they are intended under expected *in vivo* loading conditions.

7. Axial Compression Fatigue Strength of Ceramic Insert and Head

Fatigue testing was performed on the Reflection Ceramic Acetabular System to ensure that the components were capable of withstanding expected *in vivo* loading. Five of the smallest sized, thinnest inserts (28/37G) used with the smallest femoral heads (28mm +8 long) in a worst case scenario were axially fatigue loaded at 15 Hz under a sinusoidal load ranging from 1.4 to 14.0 kN (3150 lbs) for 10 million cycles. All alumina inserts loaded with alumina heads endured 10 million cycles without failure. After fatigue testing, three inserts were subjected to compressive burst testing to determine residual burst strength. Zirconia femoral heads mounted on Ti6Al4V trunnions were used for the residual burst strength testing to assure failure occurred in the inserts. The average residual burst strength for the 28 mm I.D x 37 mm O.D inserts was 47.2 kN. No specimen fractured below the 20 kN minimum cited in the Ceramic Ball guidance, thereby indicating that the Reflection® Ceramic Acetabular System is capable of withstanding the same minimum loading that the ceramic heads are expected to meet.

8. Ceramic Head/Taper Disassembly Strength (Pull-Off)

The purpose of this test was to determine if the Morse taper connection of the alumina femoral head provides adequate resistance to withstand worst case tensile pull-off forces expected *in vivo*. Five specimens of 28mm long (+8) alumina heads were assembled onto Ti6Al4V trunnions with 3 blows from a surgical mallet for pull-off testing. Testing was conducted on the most severe case i.e. head with the shortest engagement length. A static axial tensile load was applied at a rate of 2.54mm/min. The average axial distraction force exhibited by the five bearings tested was 2.26 kN, with a minimum load of 1.99 kN. This compares favorably to the average exhibited by an existing commercially available 28mm

zirconia ceramic femoral bearing (1.03 kN) and a 32mm CoCr bearing (1.08 kN). Therefore, the Morse taper connection of the alumina ceramic femoral head provides adequate resistance to withstand the worst case tensile pull-off forces expected to be encountered in-vivo.

9. Taper Cone/Head Bore Matching

Femoral stems with a 12/14 taper were evaluated by the manufacturer of the ceramic femoral components. CeramTec evaluated the compatibility of S&N 12/14 taper stems with CeramTec's BioloX Forte alumina ceramic head bore. The 12/14 tapers were found to be fully compliant with CeramTec's taper specifications to match their head bore. Therefore, components should perform as intended under expected *in vivo* loading conditions.

10. Range of Motion, Head/Liner Constraint

The Reflection® Ceramic Acetabular System does not have any linkage across the joint. It is semi-constrained in that it limits movement in one or more planes due to the geometry of its articulating surfaces. Constraint in terms of range of motion (ROM) was characterized. ROM for a 28mm ceramic head on a 12/14 taper stem articulating against an alumina ceramic acetabular insert was evaluated and compared to ROM possible for a 28mm head against a standard PE insert. The shortest and longest neck lengths for the 28mm head produced similar ROM measurements in the A/P and M/L planes when compared to the ROM possible with the PE insert. For the ceramic head/insert the A/P ROM was 139.5° for a short neck (+0) and 143° for a long neck (+8). The M/L ROM was 118° and 123°, respectively. It is noted that both the Synergy and Spectron stems utilize the 12/14 taper. By design, all neck geometries of S&N 12/14 taper stems are duplicated, so the results will be the same for either stem and are comparable to ROM values of commercially available acetabular systems.

11. Contact Area Between Head/Insert and Insert/Shell

The alumina ceramic insert and titanium shell are locked via a taper. The insert and shell are in contact circumferentially along the taper length. The insert, once press-fit and locked into the shell, is level with the face of the shell. However, the insert does not contact the hemispherical shell at the apex. Contact area between the insert and shell was calculated as ranging from 1263mm² to 1652mm² for the smallest to largest insert/shell interfaces, respectively. Contact area between the alumina ceramic head and insert was calculated as 496mm² and 808mm² for the 28mm and 32mm head/insert assemblies, respectively. Results of burst strength testing, wear testing, and taper interlock testing (see other sections), have demonstrated that the contact areas are sufficiently large for the device system to perform as intended under expected *in vivo* loading conditions.

12. Laser Etching of BIOLOX forte (SEM Analysis)

Laser etching of the alumina ceramic with a Nd-YAG 60W laser was investigated by SEM to determine any effect on the surface. Etching occurs after sintering and prior to surface grinding and finishing of the ceramic components. Very little material is removed from the surface and no microcracks were detected. Because the ceramic material is 99.7% pure alumina, it is thermodynamically stable in the alpha-alumina phase. Therefore, laser etching cannot induce a phase transformation. Results of this analysis, and the static/fatigue strength testing, demonstrate that the laser etching has no detrimental effect on the strength or performance of the ceramic components.

13. Scratched Femoral Stem Fatigue Strength (Impingement Study)

This test was performed to evaluate the effect of potential scratching of the Synergy porous coated femoral stem neck due to impingement. Although attention to cup placement and surgical skill can mitigate the chance of occurrence, impingement is sometimes unavoidable. Such a circumstance was recreated for bench testing. Five 28mm (+8) long neck length femoral head components were assembled to Synergy stems. A 10 lb static pre-load was applied to the stem and the stem's neck was positioned to impinge the ceramic insert. A worst case scratch was generated via a simulated 10 million cycle impingement. The medial position of the scratch was recommended by physicians as the most likely location for impingement to occur. Two of the five stems were then subjected to ISO 7206-4 loading conditions. Results demonstrate that the scratch had no adverse impact on the fatigue strength of the stem out to 10 million cycles. The result was consistent with theoretical calculations which indicate the inferior side of the neck region is subject to compression in-vivo and, thus, is not adversely impacted by an impingement scratch because it is not in a critical region of the construct.

14. RoughCoat™ Porous Coating Characterization (Bead Size, Bead Thickness and Static Lap Shear Strength)

The purpose of this test was to characterize the porous coating referred to as "RoughCoat™" in terms of Bead Size, Bead Thickness, Porosity and Static Lap Shear Strength. The porous "RoughCoat™" (sintered titanium porous coating from a -45+60 mesh size) had an average bead coating thickness of 1.19mm, and average bead size was 0.28mm in a 4 bead layer. The average volume porosity was approximately 32% and the average pore size was approximately 186 microns based on the two samples evaluated. Five samples of Ti6Al4V substrate with -45+60 CP titanium bead coating were prepared for lap shear testing as recommended in ASTM F1044-87. The results show that the average shear strength of the coating was 35.7 MPa (5178 psi). All failures occurred at the interface between the porous coated coupon and the non-coated coupon (i.e., the adhesive film) surpassing the recommended value of 20 MPa (2900 psi) in the

FDA Guidance Document for Testing Orthopedic Implants with Modified Metallic Surfaces Apposing Bone or Bone Cement. This characterization, in conjunction with the porous coating characterization previously provided for the sponsor's commercially available devices, demonstrates that the porous coating has adequate strength and physical properties to perform as it is intended.

15. Sterilization

The alumina ceramic femoral heads and acetabular liner components are sterilized by ethylene oxide (ETO) sterilization. The ETO sterilization process, as practiced by Smith & Nephew, is validated and subsequently revalidated periodically. ETO sterilization validation studies are conducted according to requirements of EN 550:1994/ISO 11135:1994, Medical Devices- Validation and Routine Control of Ethylene oxide sterilization. The microbiological performance qualification aspects of the validation study incorporate the half cycle of ETO sterilization validation. The validation studies yield a minimum Sterility Assurance Level (SAL) of 10^{-6} . The Reflection[®] Ceramic FSO 5 Shells, Synergy stem and Spectron stem are sterilized by gamma sterilization. The gamma sterilization process as also practiced by Smith & Nephew, is validated and subsequently revalidated periodically. The gamma sterilization validation studies are conducted according to requirements ISO 11137, "Sterilization of health care products-Requirements validation and routine control-Radiation sterilization" yielding a minimum Sterility Assurance Level (SAL) of 10^{-6} .

IX. SUMMARY OF CLINICAL TESTING

A multicenter, prospective, open-label concurrently controlled clinical trial comparing outcomes for patients randomized to either Reflection Ceramic Acetabular System (C/C) or the Reflection alumina ceramic-on-polyethylene system (C/P) as a control was conducted at 10 investigational centers by 14 investigating surgeons. The study was designed as non-inferiority trial with a 10% non-inferiority margin to evaluate the safety and effectiveness of the Reflection Ceramic Acetabular System (i.e., the success rate in the Reflection Ceramic Acetabular System group is not worse than the success rate in the active control group by more than 10%.)

Three diagnostic indications were eligible for randomized enrollment: 1) non-inflammatory arthritis (RNIA) 2) inflammatory arthritis (RIA) or 3) revision of failed implant (RR). Subsequent to completion of enrollment limit in the non-inflammatory arthritis diagnostic indication, additional subjects were enrolled in a non-randomized manner under 'Continued Access' at the same investigational centers (CAC). Device effectiveness was assessed by comparison of preoperative and postoperative changes in hip pain, function, and range of motion as measured by Harris Hip Score (HHS) tool. Pain appraisal involved the patient's current assessment of the affected hip discomfort level. Functional parameters include gait assessment of limp, support required to walk, and distance able to walk, activity assessments of ability to use

stairs, put on shoes and socks, sitting, and access transportation. Range of motion measurements included flexion, abduction, adduction, and internal and external rotation movements. Device safety was assessed by analysis of all adverse events experienced by patients in each treatment group. Pre-defined criteria were compared to determine overall success between groups

A. Study Design

Pre-defined inclusion/exclusion criteria were identified in the investigational plan. Patient randomization occurred prior to surgery, using a 1:1 randomization scheme whereby a patient (hip) was to receive either a ceramic-ceramic articulation (C/C) construct or a ceramic-polyethylene articulation (C/P) construct. Bilateral hip arthroplasty patients were randomized only once with the contralateral hip receiving the same treatment as the first hip was randomized to receive, except in one case. For each diagnostic indication group, randomization was stratified by investigational center with a fixed block size of 2. Sequentially numbered envelopes containing the randomized treatment assignment were prepared and distributed to each center. The patients and investigators were not masked to the hip system received. All x-ray films were reviewed by an independent radiologist who was not specifically advised as to treatment group prior to, or during the review. Each hip was assessed separately and followed up according to its own evaluation schedule. Patients were evaluated preoperatively to establish demographics and baseline effectiveness measurements; then intraoperatively, at discharge from the hospital, and at 3, 6, 12, and 24 months postoperatively using surrogate endpoints of pain, function, quality of life, radiographic parameters and the occurrence of adverse events to demonstrate safety and effectiveness. Patients were evaluated biennially thereafter until all patients had reached their 24 months evaluation.

1. Inclusion and Exclusion Criteria

Inclusion Criteria

Patients meeting all of the following inclusion criteria were enrolled in the study:

- Primary diagnosis of osteoarthritis, rheumatoid, or revision
- Males or females, 21-80 years old
- Able to follow-up for 2 years
- HHS ≤ 60
- Preoperative medical clearance; free or treated for cardiac, pulmonary, hematological conditions that pose excessive operative risk
- Meets no exclusion criteria

Exclusion Criteria

Patients who met one of the exclusion criteria were not eligible for enrollment in the study:

- Morbid Obesity ≥ 100 pounds over desirable body weight

- Insufficient bone from cancer, femoral osteotomy, Girdlestone, osteoporosis, metabolic disorders
- Charcot joint, muscle deficiencies, multiple joint disabilities
- Active localized or systemic infection
- Skeletal immaturity
- Psychological illness, mental illness, mental retardation, or drug, alcohol abuse
- Pregnancy
- Immunosuppressive disorder: corticosteroid use[§], cytotoxic drugs, antilymphocytic serum, irradiation, AIDS, immunosuppressive therapy, auto immune diseases (except rheumatoid arthritis). [§]Patients using 0.1 to 80 mg/day were not excluded in this study.
- Subject participating in any other pharmaceutical, biologic, or medical device clinical investigation
- Known sensitivity to the materials in the device -

2. Clinical Assessment

Clinical patient evaluations were performed preoperatively, intraoperatively, and at discharge. Evaluations were also performed postoperative at 3 months, 6 months, 12 months, and 24 months and biennially thereafter for any applicable patients. Preoperatively, patient demographics and basic medical history was collected. Patient outcomes were evaluated for the involved hip using a modified Harris Hip Score Scale* a rating scale that incorporates subsections relating to hip pain; functional gait and activities of daily living; deformity and range of motion. The Harris Hip Score scale scoring ranges from 0 (worst) to 100 (best). A modified Harris Hip Score was used, which allowed simpler calculation of range of motion results. A patient self-assessment (SF-12) general health survey was administered to collect quality of life outcome information also. Intraoperatively, information was collected that consisted of the surgical technique performed, any intraoperative or perioperative complications/adverse events which may have occurred and any other relevant implant-related information needed to characterize the performance of the device. At discharge, patients were assessed for ambulatory status and incidence of adverse events since surgery. Discharge x-rays served as the baseline radiographic assessment for later comparisons. A/P and Lateral radiographs were assessed for implant position and evidence of radiolucencies. Clinical evaluations were standard at each postoperative interval. Each postoperative visit consisted of a Harris Hip Score evaluation, radiographic assessment and SF-12 Health Survey. Any adverse event occurring since the previous visit evaluation interval was recorded. At some early intervals (3 months), collection of radiographs and SF-12 surveys were optional. Site investigators were responsible for assessing patients at all intervals. For the 24 month interval, radiographs were also independently evaluated by a radiologist.

* Canale, T., editor. Campbell's Operative Orthopaedics. St. Louis: Mosby, Inc.; 2003.

3. Success Criteria

The primary endpoint of the clinical trial was an overall patient success outcome determination at 24 months, which included a composite of implant survivorship, Harris Hip Score, and radiographic evaluation. A successful patient at 24 months met all of the following required criteria:

- no revision of any device system component through the two years evaluation;
- a total Harris Hip Score greater than or equal to 80 (excellent to good score); and
- no evidence of unacceptable radiolucencies or position change along the cup and stem (radiographic failure) as defined by exhibiting radiolucencies of:
 - a. greater than 50% of the total bone prosthesis interface; and/or
 - b. greater than or equal to 2 millimeters in two or more zones; or
 - c. if the patient has subsidence of the femoral stem or migration of the acetabular prosthesis of greater than 5 millimeters with associated clinical findings.

The success criteria were used to assess the overall treatment success for the study device versus control device populations. Patients (hips) were categorized as a success or non-success, and the comparison between the two treatment groups is indicative of the devices performance in the study populations.

4. Statistical Analysis

The randomized non-inflammatory arthritis cohort (RNIA) represented over 80% of the total hip replacements performed in the study; therefore, any statistical testing between device groups were only performed for this cohort at the 2-year visit. For the other two diagnostic groups, only descriptive statistics were generally provided.

The safety and effectiveness of the Reflection Ceramic Acetabular System was assessed by analyzing the Patient Success Criteria, which include revision status, functional/clinical evaluation, and radiographic assessments. A non-inferiority hypothesis was used to test the difference in the probability of patient's success with a 10% margin. The null hypothesis was the success outcome rate at 2 years in the control group is greater than the success rate in the study device group by at least 10%, and the alternative hypothesis is that the difference in success rates between the two groups is less than 10%. The null hypothesis will be rejected if the upper bound of the two-sided 90% confidence interval (CI) for the difference in success rates is less than 10% and conclude that the study device is non-inferior to the control. A logistic regression model and GEE model for the success outcome at 2 years were also performed to evaluate the effect of device group, body mass index, age, gender, type of hip replacement (unilateral vs bilateral), femoral stem cement use (yes vs no) and investigational site.

Additionally, the risk of ceramic-ceramic articulation was assessed by analyzing the revision rate by two years, applicable operative and postoperative adverse events (device related or otherwise); Survivorship analysis was assessed using Kaplan-Meier methodology.

Results on hip pain, function, and range of motion were also compared between the study and control groups using Wilcoxon rank sum test. The incidence of radiographic failures were compared between the two groups using Fisher's Exact Test. Fisher's Exact Test was also used to compare the percentage of patients reporting each type of adverse event between the two device groups. Multiple occurrences of the same event reported by the same patients were counted as only once. Results from SF-12 health survey at 2 years were compared using a two-sample t-test.

B. Study Population/Demographics

In total, 399 patients were implanted with 460 devices in the investigational study under the study protocol at 10 investigational sites by 14 investigating surgeons. One patient was counted twice as the patient had one of each device implanted in each of his hips. In the randomized non-inflammatory arthritis (RNIA) study cohort, there were 146 patients who received the investigational device and 130 patients who received the control device at 10 investigational sites. In the inflammatory arthritis cohort, there were 14 patients at 7 investigational sites who received the investigational device. In the revision cohort, 5 patients received the investigational device at 4 sites. All patient cohorts were evaluated in the safety analysis. Effectiveness was based on only the RNIA cohort.

For all RNIA subjects enrolled, males accounted for 114/174 (65.5%) and 84/141 (59.2%) in the study and control groups, respectively; and the mean body mass index was 28.9 and 28.1 kg/m² in the study and control groups, respectively. The mean age at surgery as determined from a patient analysis was 50 years and 54.3 years in the study and control groups, respectively; and difference in average age between the two groups is significantly different (p-value 0.0121, Wilcoxon rank sum test). The two treatment groups were very similar demographically, and there were no statistically significant (p < 0.05) differences for any of the other variables. Ethnic demographic data was not collected. There was a predominance of male patients; younger patients and more bilateral patients were enrolled in the investigational group. The demographics of the randomized non-inflammatory arthritis cohort as determined from an all Hip analysis are detailed in Table 1.

Table 1, Demographics- All Hips

Description of the Study Populations							
	Non-Inflammatory RNIA		Inflammatory RIA		Revision RR		Continued Access CAC
	C-C	C-P	C-C	C-P	C-C	C-P	C-C
Number of hips/ (patients)*	174 (146)	141 (130)	17 (14)	13 (10)	5(5)	7(7)	103 (88)
Bilateral hips (%)	57 (33%)	23 (16%)	6 (35%)	6 (46%)	0	0	30 (29%)
Men / Women	114/60	84/57	10/7	4/9	3/2	4/3	60/43
Age, year (mean)	50	53.9	47.6	44.3	50	62.7	46.2
Age < 40	23.5%	11.5%					
40 ≤ Age ≤ 69	70.3%	74.6%					
Age > 69	6.2%	13.9%					
Height (cm)	173.9	172.7	166.1	169	174.8	170	173.1
Weight (Kg)	87.6	84.3	77.8	78.3	89.2	77.4	86.3
BMI (kg/m ²)	28.8	28.1	28.5	27.4	29.4	26.9	28.7
Previous surgery on Affected hip							
YES	33	23	2	0	5	7	21
NO	141	118	15	13	0	0	82
Other joint involvement: YES	107	83	14	10	3	4	47
NO	67	58	3	3	2	3	56
Physical Activity							
None	12	4	0	0	2	1	7
Light	107	94	13	12	3	5	66
Moderate	50	37	4	1	0	0	27
Intense	5	6	0	0	0	0	3

*one patient was counted twice because the patient had one of each device implanted in each of his hips

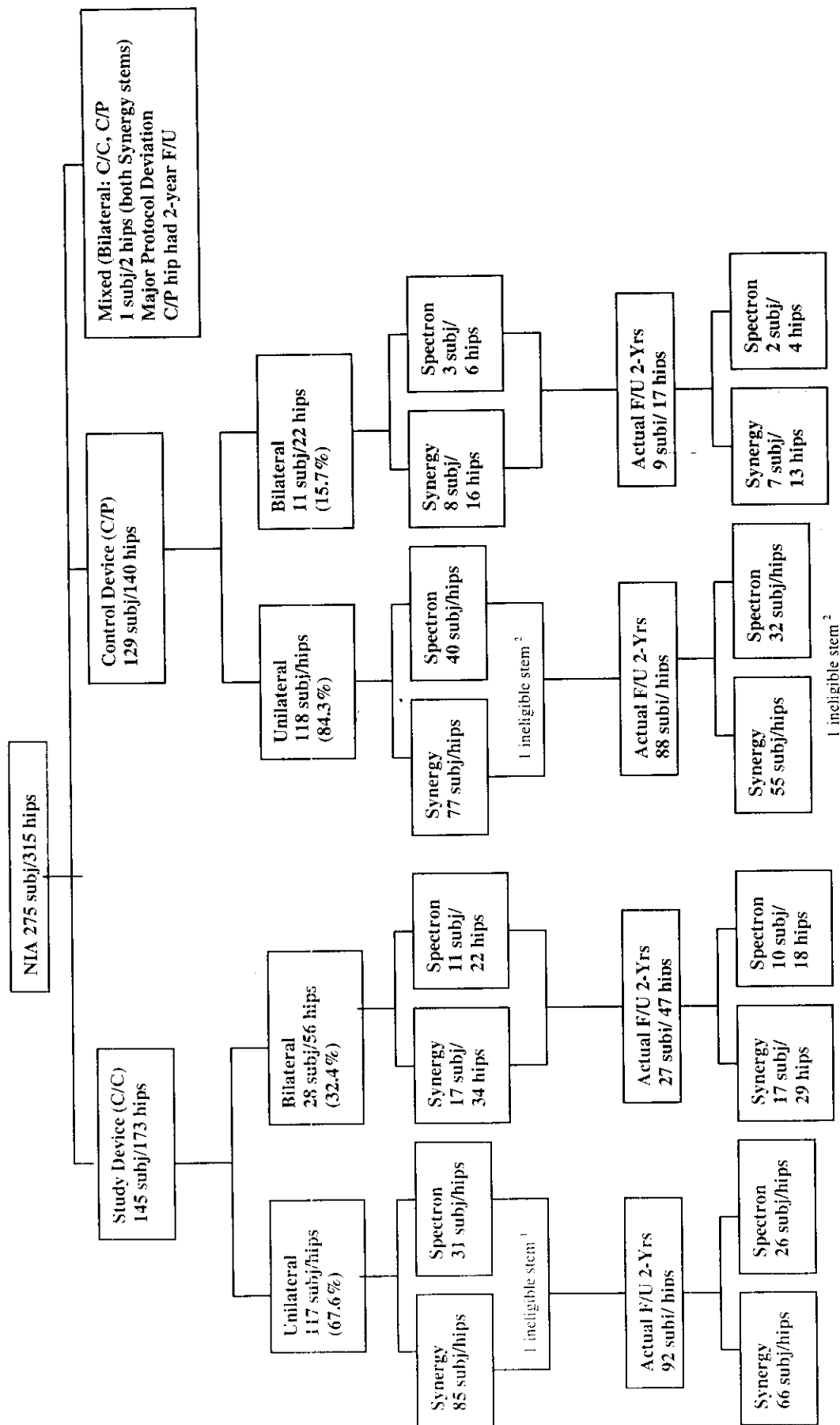
C. Hip/Patient Accountability

Accountability of numbers of hip and patients analyzed is shown in the following flow chart entitled, “Flowchart, Patient (Hip) Accountability RNIA Cohort All Hips” and in Table 2 below for the RNIA cohort as this is the primary study group. Note that eighteen ceramic-ceramic hips and twenty-five ceramic-poly hips were identified as either minor or major protocol deviations, and these hips are excluded from the efficacy analysis. This resulted in 156 ceramic-ceramic hips and 116 ceramic-poly hips analyzed for effectiveness in the RNIA cohort at 2 years.

Discontinued Patients

At the 2 years evaluation interval, there were 86 hips that were discontinued during the course of the study (70 hips in the RNIA, 9 hips in the RIA, 7 hips RR). Discontinued refers to hips that did not have clinical follow-up at two years due to any reason, i.e. lost to follow-up, dead, revised, not yet due for follow-up at 2 years, etc.

Flowchart, Patient (Hip) Accountability RNIA Cohort All Hips



¹ Study device hip (Entry ID 163) was implanted with an ineligible stem, a Synergy cemented stem

² Control device hip (Entry ID 038) was implanted with an ineligible stem, a Spectron 14/16 stem

Table 2, Hip Procedure Follow-up Accountability – Per Protocol RNIA Cohort

Category	Preop		3-months		6-months		1-year		2-years		2+ years	
	C/C	C/P	C/C	C/P	C/C	C/P	C/C	C/P	C/C	C/P	C/C	C/P
Theoretically Due¹	156	116	156	116	155	116	154	116	150	116	150	116
Deaths*	0	0	1	0	1	0	1	0	0	1	1	0
Revisions	0	0	2	1	1	0	0	0	1	0	2	0
Expected²	156	116	153	115	151	115	150	115	145	114	145	114
Evaluated³	156	116	142	104	137	99	128	94	126	85	128	85
Actual Follow-Up %	100%	100%	92.8%	90.4%	90.7%	86.1%	85.3%	81.7%	86.9%	74.6%	88.3%	74.6%

C/C = ceramic-ceramic; C/P = ceramic-polyethylene

Note: Modified Per Protocol analysis excludes all major and minor deviations from the investigational plan
(C/C: 174-18 protocol deviations = 156, C/P: 141-25 protocol deviations = 116)

¹ Theoretically due is the number due at each interval based on the date of surgery and date of database closure.

² Expected is the number theoretically due minus cumulative deaths and revisions.

³ Evaluated is actual Total Harris Hip Score or Function Score obtained but the number excludes evaluations on previously revised hips.

* Deaths post-revision are not subtracted from Theoretically Due to achieve Expected. 2 patients (hips) died after revision. In C/C group, there are 7 cumulative deaths and revisions through 2 years, and thus only 5 hips are subtracted from Theoretically Due at 2 years.

At the completion of the study there had been four deaths in the RNIA investigational group and one in the control group. No other deaths occurred in any of the other cohorts or in the continued access cohort. Revision surgery was performed in 6/156 (3.9%) RNIA hips in the investigational and 2/116 (1.7 %) hips in the control group. One revised RNIA C/P hip was a protocol deviation that is not reflected in the per protocol accounting of Table 2. Revisions occurred in 1/17(5.9%) of hips in the RIA cohort, 0/5 (0%) of the hips in the Revision cohort, and 5/103 (4.8%) of the hips by one year in the CAC cohort. There were no revisions in the control groups of the RIA or Revision cohorts. At 24 months, 126 hips were evaluated in the RNIA investigational group and 85 hips were evaluated in the control group. Since the overall success criteria was based on a three part composite of revision status, clinical function, and radiographic results at two years, some hips may be evaluated at two years but still be missing one or more components of the three components. However, at two years, there were 122 hips in the ceramic-ceramic group and 81 hips in the ceramic-poly group with all three components necessary to evaluate success. At the time of data base closure no patients in the continued access cohort had reached the 24 month evaluation interval.

D. Study Period

The first patient was implanted in November of 1998. All patients in the randomized non-inflammatory arthritis cohort had reached their 24 month postoperative period as of the data base closure on February 24, 2003. However, the second hip replacement in 7 investigational device patients was not yet due at 2

years follow-up. With 2 year follow-up required on all patients, the total duration of this study was 4.25 years. A change to the device was made on April 17, 2001, which redesigned the accepting shell/cup to have a chamfered edge in an attempt to reduce the potential cracking, chipping, fracture or other damage to the ceramic liner upon insertion. This design change would not have significant impact on the results of the clinical trial.

E. Safety and Effectiveness Data

1. Safety Data

Safety was determined through the comparison of adverse event rates both device related and unrelated, implant survival, and radiographic analyses for all patients, randomized or non-randomized, receiving the device. In the total enrolled population, there were 4 intraoperative revisions due to liner chipping upon insertion, and 12 postoperative revisions in 299 hips implanted (for any indication and including the Continued Access hips – see Table 1) with the ceramic on ceramic hip system. One intraoperative revision due to instability and 2 postoperative revisions in 161 hips occurred with the control device.

The rate of specific adverse events, particularly, revisions, HO, dislocation, and proximal linear femur fractures were higher in the investigational group for all hips in the RNIA cohort.

Revisions

In the RNIA cohort, six postoperative revisions in 174 hips (3.4%) occurred in the C/C group. Two hips revised at three months due to dislocation in one hip and infection in the other case. One hip was revised at six months due to recurrent dislocations. At two years or greater, revisions were required for one hip with a fractured ceramic femoral head, one hip with a fractured ceramic acetabular liner, and one hip with a loose femoral component. Two postoperative revisions in 141 hips (1.4%) occurred in the C/P RNIA group. Revision was required in the discharge period for one hip due to instability, and one hip at three months due to an infection (Table 4). The estimate of the proportion of hips without revision at two years, in the RNIA cohort was 98% (95% CI: 95%-100%) for the C/C group and 99% (97%-100%) for the C/P group. The revision free-survival was not statistically significantly different between the two groups (Log- rank test, $p=0.3438$).

In the Continued Access population of 103 hips, five hips (4.9%) were revised by 1 year. One hip was revised at 3 months for prolonged dislocation. Two hips were revised at 6 months (one hip for dislocation and one hip for loose stem). At one year or more, two hips were revised due to one infected hip and one case of osteolysis. One ceramic-ceramic hip in the RIA cohort was revised at 6 months due to stem subsidence. There were four hips revised

intraoperatively due to liner chipping during insertion that required immediate cup/liner exchange.

The revision rate for this study to date is 16/299(5.4%) hips (see Table 1) with revisions in the C/C group at all evaluation intervals for all cohorts. The rate for the RNIA Cohort C/C group is 8/134 = 6% (174 – 40 hip exclusions) and is 8/174 = 4.6% without hip exclusions. The rate for the RNIA Cohort for the C/P control group is 3/102 =3% (141 – 39 hip exclusions) and is 3/141=2.1% without hip exclusions. The rate for the non-inflammatory Continued Access cohort is 7/103 =6.8% at 1.5 years, with incomplete follow-up at 2 years (1 hip with a revision at 2 year window included).

Table 3, Revised Hips – RNIA Cohort

Treatment	Interval	Reason for Revision	Components Revised
C/C	Intraop	chipped liner	Cup, liner
C/C	Intraop	chipped liner	Cup, liner
C/C	3 month	Dislocation	Liner, head
C/C	3 month	Infection	All components
C/C	6 month	recurrent anterior dislocations	Cup, liner, head
C/C	2 year	ceramic head fracture	Liner, head
C/C	Post 2 year	ceramic liner fracture	Cup, liner, head
C/C	Post 2 year	Loose femoral component	head, stem
C/P	Intraop ;	Instability	Liner
C/P	Discharge	Instability	Liner, head
C/P	3 months	Infection	All components

C/C=ceramic-ceramic; C/P=ceramic/polyethylene

Heterotopic Ossification

The overall incidence of heterotopic ossification was found as follows in Table 4 for the RNIA Cohort.

Table 4, Incidence of Hips with HO- RNIA Cohort

HO *	C/C (N=174)	C/P (N=141)
Grade I	36 (20.7%)	31 (22%)
Grade II	7 (4%)	3 (2.1%)
Grade III	7 (4%)	2 (1.4%)
Grade IV	1 (0.6%)	0 (0%)

* Brooker Classification

Dislocations

There were 25 dislocations reported for this study for all cohorts at all intervals. Of these, 11 events (4 intraoperative and 7 postoperative) occurred in 7 hips in those patients randomized to the ceramic-poly group. In the ceramic-ceramic group, there were 14 postoperative dislocation events in 9 hips. A majority of

the dislocations (7 hips /10 events) in the ceramic-ceramic hips occurred in the first 3 months.

Proximal linear femur fractures

These events occurred intraoperatively in 7 ceramic-ceramic hips, 4 in the control group and 3 in the continued access group. All fractures occurred during preparation of the femoral canal or during actual stem insertion.

Adverse Events by time of occurrence

Within the RNIA cohort, there were a total of 34 intraoperative Operative Site adverse events that were seen in 17/174 hips (9.8%) that received the Reflection Ceramic Acetabular device and 8/141 hips (5.7%) in the control group. The intraoperative, Operative Site adverse events that occurred most frequently in the ceramic-ceramic group were proximal medial linear split (bone) fracture in 7/174 hips (4.0%), blood loss greater than 1500 ml in 6/174 hips (3.4%) and difficulty implanting the alumina ceramic acetabular liner in 2/174 hips (1.1%). Other events reported once (1/174=0.6%) were insufficient bone stock, nerve injury, and trochanteric fracture. The rate of events was comparable to the control group with the exception of difficulty implanting a ceramic liner.

In the RNIA cohort, 117 postoperative Operative Site Adverse Events were reported in 62 hips in the C/C study group, as compared to 72 events in 45 hips in the C/P group. The postoperative complications involving HO Grades I, II, and/or II, dislocation, incisional drainage, trochanteric bursitis, hematoma, DVT/PE, deep infection ≤ 6 weeks, superficial infection, and revisions (partial or complete) were the most frequently reported adverse events in the ceramic-ceramic group. The rates of these adverse events, when directly compared to the rate in the control group, did not demonstrate a statistically significant difference.

In the RNIA cohort, 54 C/C patients had a total of 95 postoperative systemic adverse events during the discharge interval through the post 2 year interval. 52 control patients had a total of 83 postoperative systemic adverse events. The most common systemic adverse events observed in both groups were related to the skeletal system. Nineteen of 146 (13%) patients reported 26 events and 22/130 (17%) patients reported 25 events related to the skeletal system in the C/C and C/P groups, respectively.

In the RNIA cohort, the other most frequently reported postoperative systemic adverse events in C/C patients were related to circulatory, digestive, integumentary, nervous, cardiac, muscular, or urinary systems. Rates of these and falls, anemia, deaths, DVT, PE, and surgery of the involved hip (but not affecting the implant) occurred with a frequency of between 1.4% (2/146 patients) and 6.2% (9/146 patients). DVT, PE occurred with greater frequency in the investigational group (2 patients) but none were reported in the control

group. Intraoperatively, one incidence of hypoxia occurred in a bilaterally implanted C/C patient, and one incidence of hypotension occurred in a C/P patient.

In the RNIA cohort, the systemic postoperative adverse events in the C/C patients included allergic reaction, motor vehicle accident, pneumonia, electrolyte, hepatobiliary, renal, or respiratory abnormalities which occurred at a rate of 0.7% (each event reported once in 146 patients).

In the RNIA cohort, the operative site postoperative adverse events in the C/C hips included audible squeak in the hip, pelvic fracture, delayed wound healing, heterotopic ossification grade IV, I&D local, femoral head fracture, acetabular liner fracture, loosened stem, insufficient bone stock, head migration, and head subluxation which occurred at a rate of 0.6% (each event reported once in 174 hips). The majority of these appear to be device- or procedure-related.

Deaths

There were 6 deaths during the course of this study; 5 in the C/C group and one in the C/P group. All were in the RNIA cohort. One patient who died was a protocol deviation that is not reflected in Table 2 - Hip Accounting. Three of these patients in the C/C group died at, or prior to, the 1 year follow-up: one within the 18 days post operatively, and one 4 months post operatively, one at one year postoperatively. Two patients, died at the time of the 2 year or greater follow-up. In the C/P group, the patient died at the 2 year postoperative time point. Three patients' deaths (house fire death, 2 deaths due to lung cancer) in the C/C group and the one C/P group patient (heart disease) are clearly not related to the procedure or the device. The remaining 2 deaths occurred close to the surgical procedures associated with confirmed or suspected sepsis after revision or dislocation events.

Operative Site and systemic adverse events as well as revisions occurring in RNIA population are provided in time course adverse event distribution Tables 11-15 at the end of this document.

Summary of Safety

Patients in the Reflection ceramic group experienced more adverse events associated with the implant or procedure than the control group did, however this difference was not statistically significant.

There are different adverse events associated with the ceramic couple specifically liner fractures. The reasons for revision are similar with that anticipated of any total hip prosthesis (dislocation, infection, bone loss, component loosening/migration) except for intraoperative chipping of the ceramic liner that required cup/liner exchange and postoperative ceramic component fractures requiring revision. In this study, a higher incidence of heterotopic ossification was observed.

Treatment Results

For the RNIA cohort, mean operative time and blood loss were similar. The majority of bilateral procedures in both groups were staged procedures although more patients in the investigational group had same day bilateral surgeries (24) than in the control group (8). A posterior lateral approach was the most common surgical approach to the hip. In the investigational group the left hip and in the control group the right hip was implanted more frequently. The Synergy hip stem was used in 120 investigational hips and 94 hips in the control group. The Spectron EF stem was used as part of the construct in 53 investigational hips and 46 control hips. Bone graft was not used in the majority of patients in either group. When bone graft was used, the acetabulum was the site grafted most in both treatment groups. In the majority of procedures no cement was used to fix the components. When cement was used, the femur was cemented in 54 and 47 procedures in the investigational and control groups respectively.

2. Effectiveness Results

Success outcome is based on a three part composite at the two years interval, whereby the hip had not undergone revision, had Total Harris Hip Score greater than or equal to 80, and no radiographic failure due to unacceptable radiolucencies or component subsidence/migration. Radiographs were evaluated by an independent radiologist at 24 months only.

RNIA Cohort preoperative baseline effectiveness evaluations on the HHS, ROM, and SF-12 were similar between the two groups (Table 5).

Table 5, Baseline Evaluations - RNIA Cohort

Baseline Evaluations		
	RNIA C/C	RNIA C/P
Harris Hip Score (100 pts)	44.6	43.8
HHS Pain score (44 pts)	13.5	13.6
HHS Function score (47 pts)	24.3	23.3
ROM Flexion (degrees)	86.3	84.2
SF-12 PCS	29.5	28.7
SF-12 MCS	52.2	51.6

Table 6 provides a summary of Success Outcome for the two study groups (per protocol analysis).

Table 6, Effectiveness Results and Success Criteria at Two Years Per Protocol¹

Category	2-year results						1-year results
	RNIA		RIA		RR		CAC
	C/C	C/P	C/C	C/P	C/C	C/P	C/C
Enrolled *	174	141	17	13	5	7	103
Evaluated ^A	126	85	12	6	2	1	53
Mean Harris Hip Score (Total 100)	96.0 (n=126)	92.6 (n=85)	92.8 (n=12)	88.3 (n=6)	98.5 (n=2)	71.0 (n=1)	95.3 (n=53)
Revision Success (hip not revised)	122/126 (96.8%)	84/85 (98.8%)	11/12 (91.7%)	6/6 (100%)	2/2 (100%)	1/1 (100%)	49/53 (92.4%)
Harris Hip Success (≥ 80)	121/126 (96.0%)	76/85 (89.4%)	11/12 (91.7%)	5/6 (83.3%)	2/2 (100%)	0/1 (0%)	49/53 (92.5%)
Radiographic Success ^B	118/118 (100%)	77/78 (98.7%)	12/12 (100%)	6/6 (100%)	2/2 (100%)	1/1 (100%)	50/50 (100%)
Overall Success ^C	113/122 (92.6%)	70/81 (86.4%)	11/13 (84.6%)	5/6 (83.3%)	2/2 (100%)	0/1 (0%)	46/54 (85.2%)

¹ Per protocol patients evaluated at 24 months

* Enrolled is the number of hips implanted in the study by cohort.

^A The number of evaluated, non-revised hips with an actual Total Harris Hip Score obtained at the 2 years follow-up. Partial evaluations not included in table.

^B Denominator is the number of actual independent-read radiographs and not the number with any evaluations.

^C Denominator is number of failures plus the number of hips with independent-read radiographs that were judged a success in the per-protocol population at 24 months.

Results of multivariate regression analyses (logistic regression model and GEE model) justified the pooling across centers, hip replacement (bilateral/unilateral) and femoral stem cement use (yes/no). There was no statistically significant effect of age, gender or body mass index on the success outcome at 2 years. The adjusted odds ratio of success for C/C compared to C/P based on the logistic regression model (hips with missing data at 2 years were excluded) was 1.8 (95% CI: 0.8-4.3).

The study device group (C/C) was demonstrated to be at least as good as the control (C/P) with respect to the success rate among all hips with complete data regardless of whether or not there was a protocol deviation at 2 years (C/P: 85/102=83.3% (141 – 39 hip exclusions) vs. C/C: 123/134=91.8% (174 – 40 hip exclusions) and the upper bound of one-sided 95% CI for the difference was less than 10%). Sensitivity analyses (e.g., last observation carry forward) including all the randomized hips showed that the missing data at 2 years did not change the conclusion that the Reflection Ceramic device (C/C) was not inferior to the control. Based on this analysis the effectiveness data in Table 6 reflects the outcomes of the population studied.

The overall success outcome reported in Table 6 incorporates elements of effectiveness. Other clinical measurements of clinical effectiveness are summarized in Table 7 for the RNIA cohort.

Table 7, Time Course Effectiveness and SF-12 Health Survey Physical Scale - all Hips (RNIA)

	<u>Preop</u>		<u>3 Months</u>		<u>6 Months</u>		<u>12 Months</u>		<u>24 Months</u>	
	<u>C/C</u>	<u>C/P</u>	<u>C/C</u>	<u>C/P</u>	<u>C/C</u>	<u>C/P</u>	<u>C/C</u>	<u>C/P</u>	<u>C/C</u>	<u>C/P</u>
N	174	141	157	127	151	120	144	115	139	106
Total Harris Hip Score Mean ¹	44.6	43.8	84.2	86.2	90.8	92.1	93.9	92.9	95.6	92.1
(SD)	(10.7)	(9.7)	(14.4)	(13.6)	(13.1)	(10.6)	(9.0)	(10.8)	(7.5)	(10.5)
Total Harris Hip Pain Subscore Mean ² (SD)	13.5 (4.9)	13.6 (5.0)	37.7 (8.3)	38.8 (7.9)	39.8 (7.5)	40.9 (6.2)	41.0 (5.8)	41.1 (6.2)	42.2 (4.6)	40.5 (6.5)
Total Harris Hip Function SubScore Mean ³ (SD)	24.3 (7.6)	23.3 (7.4)	38.1 (7.9)	38.9 (7.3)	42.4 (6.5)	42.4 (6.4)	44.1 (5.0)	43.1 (5.7)	44.6 (4.5)	42.8 (6.1)
Flexion (degrees) Range of Motion Mean (SD)	86.3 (18.4)	84.2 (22.3)	102.2 (14.5)	104.7 (13.5)	109.0 (15.5)	110.6 (15.8)	109.9 (16.7)	110.3 (16.2)	111.8 (15.6)	112.1 (16.6)
SF-12 Health Survey Physical Scale Score Mean ⁴ (SD)	29.5 (7.5)	28.7 (7.3)	41.9 (9.9)	41.9 (9.4)	48.2 (9.4)	47.9 (8.9)	49.2 (9.0)	48.3 (9.3)	49.5 (8.6)	47.1 (10.3)

C/C=Ceramic-Ceramic group, C/P = Ceramic-Poly group

1 Total Harris Hip Score scale from 0 (worst) to 100 (best)

2 Harris Hip Pain Sub-Score scale from 0 (worst) to 44 (best)

3 Harris Hip Function Sub-Score scale from 0 (worst) to 47 (best)

4 The mean of the Physical Component Summary scale in the general U.S. population is 50±10

Effectiveness Conclusions

Clinical results in the RNIA cohort shows improvement in overall and subscore Harris hip scores indicating improvement in pain and function over the course of the study, with approximately 90% of the patients in the evaluated group with good to excellent results, with few radiographic failures, acceptable implant survival at 2 years comparable with the control and that in the conventional hip implant literature, and improved physical quality of life scores on the SF-12 health survey. Range of motion improved in both groups as compared to preoperative measurements, but were not statistically significant. Overall success rates are no worse than the control.

F. Clinical Results in Other Diagnostic Cohorts

The results presented in previous tables are specific to patients with a primary diagnosis of non-inflammatory arthritis of the involved hip. The clinical study also permitted enrollment of patients with inflammatory arthritis or patients requiring revision surgery for other hip devices that have failed. Patients were

subject to the same inclusion/exclusion criteria and the same investigational plan as the RNIA cohort. Results are provided in Table 8.

Table 8, Patient Accounting at 2 Years-RIA, RR and CAC Cohorts

	Inflammatory Arthritis RIA		Revision RR		Continued Access CAC	
	C-C	C-P	C-C	C-P	1yr	2yr
Theoretically Due	16	13	4	6	81	-
Deaths*(cumulative)	0	0	0	0	0	-
Revisions (cumulative)	1	0	0	0	4	1
Expected	15	13	4	6	77	-
Actual	12	9	2	3	60	1
Missing	3	4	2	3	17	-
Follow-up %	80	69.2	50	50	77.9	-

Summary of Inflammatory, Revision and Continued Access cohorts

In the randomized inflammatory arthritis cohort (RIA), data were collected from 17 hips (14 patients) implanted with the ceramic-ceramic device while 13 hips (10 patients) received the ceramic-poly device. In the randomized revision cohort (RR), data were collected from 5 hips (5 patients) implanted with the ceramic-ceramic (study) device while 7 hips (7 patients) received the ceramic-poly (control) device. The data from the inflammatory arthritis and revision cohorts is insufficient to make absolute statements regarding safety and effectiveness in these diagnostic indications. However, the patient outcomes in these populations showed a trend toward significant clinical benefit; relief of pain and return to function as measured by the Harris Hip Score, outweighing the risks of surgery in this population. At the time of database closure, no patients in the Continued Access Cohort had reached their theoretical 2 year follow-up interval. Therefore, results at one year were used for safety information. Data collection continues for this cohort.

Randomized Inflammatory Arthritis Cohort Adverse Events

No systemic adverse events were reported in the intraoperative interval. Intraoperatively, one patient experienced a proximal medial linear split fracture in the C/C group. In the C/P group there was difficulty implanting the cup, dislocation of the head, revision of cup and liner. Skeletal events occurred in 1 hip in the ceramic/ceramic group and 4 events and in 4 hips in the control group. In the ceramic group, 1 hip was noted to show subsidence and migration of the stem at 3 months. Revision of the femoral head and stem was undertaken at 6 months.

Randomized Revision Cohort Adverse Events

No intraoperative systemic adverse events were reported. Intraoperative operative site events consisted of >1500 ml blood loss and a proximal medial

linear split fracture both occurring in the C/P group. Postoperative systemic events included anemia, (1 event in the investigational and 2 in the control). Postoperative Operative Site complications included heterotopic ossification grade I (1 investigational hip at 3 months), and nerve injury (1 control hip at discharge). There were no complications of device component migration, fracture, loosening, subluxation/subsidence and no intraoperative or postoperative complications were considered device related. There were no revisions in this cohort.

Continued Access Non- Inflammatory Cohort

In the Continued Access cohort 5 postoperative revisions were reported in 103 hips (4.8%). Two liners chipped during impaction which required revision of liner and cup intraoperatively. Of the 5 postoperative revisions, 3 revisions occurred within 6 months, and 1 revision at 1 year and 2 years each. Reasons for revision included dislocation (2), loose stem (1) infection/loose cup (1) and osteolysis (1). One hip had increased blood loss (2300cc). Postoperative revisions and loosening occurred in 5 patients. Revisions are detailed in Table 9, and a time course of adverse events is provided in Table 10.

Table 9, Hips Revised - Continued Access Cohort

Treatment	Interval	Reason for Revision	Components Revised
C/C	3 month	prolonged dislocation/soft tissue laxity	head
C/C	6 month	recurrent posterior dislocations	stem
C/C	6 month	subsidence/loosening of stem	head, stem
C/C	1 year	infection/loosened cup	cup, liner
C/C	2 years	Osteolysis	head, stem

C/C=ceramic-ceramic

Table 10, Time Course of Operative Site Adverse Events - Continued Access Cohort

Events	IO	DC	3M	6M	12M	24M	36+mos	Total
Total events	12	1	9	6	4	2	0	34
# hips	103	103	87	82	61	1	0	103
Blood Loss>1500ml	1							1
Cardiac Arrhythmia	1							1
Difficulty Implanting liner	1							1
Dislocation Head			3	1				4
Fracture Liner	2							2
Hematoma			1					1
HO Grade I			1					1
Loosened cup				1				1
Loosened stem				1				1
Inc drainage			1					1
Infection Deep<6wks			1					1
Infection Deep>6weeks					1			1
Nerve Injury		1						1
Osteolysis					1			1
Proximal medial linear split FX femur	3							3
Revision: cup	2				1			3
Revision head			1	1		1		3
Revision liner	2				1			3
Revision: stem				2		1		3
Sublux./Subside. Stem			1					1

IO=intraoperative; DC=discharge; 3M= 3 months; 6M= 6 months; 12M= 12 months; 24M= 24 months; 36+M= post 24 months. Excludes adverse events after the first revision of a C/C device.

Safety

As with the RNIA cohort, the preliminary safety data for the RIA, RR, and CAC cohorts indicate that there are certain adverse events associated with the brittle material and different implantation techniques as compared to the conventional hip systems. The data suggest there are specific patients who had less successful outcomes (less successful HHS) including those who were protocol deviations in this study, (e.g. weight above recommended BMI), and those with preoperative/intraoperative risk factors including noncemented components, male gender, prior surgery, prior ectopic bone, anterolateral surgical approach, complexity of surgery. These suggest that specific patient and intraoperative selection criteria be advised. The data related to the formation of Heterotopic ossification suggest a recommendation for prophylaxis in those conditions, even in primary hip arthroplasty.

Effectiveness

The absolute effectiveness data for the RIA cohort cannot be determined due to the small sample size; however preliminary data shows that the Reflection

Ceramic Acetabular System device used in the treatment of inflammatory arthritis of the hip may improve the majority of patients' pain and function with improved physical quality of life as measured by the HHS, SF-12.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Safety

Patients in the Reflection ceramic group experienced more adverse events associated with the implant or procedure than the control group did, however this difference was not statistically significant.

There are different adverse events associated with the ceramic couple, specifically liner fractures as compared to conventional hip designs. The reasons for revision are mostly similar to those anticipated for any total hip prosthesis (dislocation, infection, bone loss, component loosening/migration) except for intraoperative chipping of the ceramic liner that required cup/liner exchange and postoperative ceramic component fractures requiring revision.

Recognizing the potential contribution of design and intraoperative surgical technique associated with the intraoperative adverse events, a change to the device was made on April 17, 2001, which redesigned the accepting shell/cup to have a chamfered edge in an attempt to reduce the potential cracking, chipping, fracture or other damage to the ceramic liner upon insertion. Of the 299 C/C hips implanted in the study, 288 C/C hips were implanted with the original shell design (with 4 intraoperative chipping events); and 11 C/C hips (2 in RNIA cohort and 9 in CAC cohort) have been implanted with the modified shell (chamfer) design. Since the modification, the surgical technique has emphasized the avoidance of direct contact percussion to the liner; and there have been no reports of intraoperative chipping of the ceramic liners with the modified shell.

Effectiveness

Clinical results in the RNIA cohort shows improvement in overall and subscore Harris hip scores indicating improvement in pain and function over the course of the study, with approximately 90% of the patients in the evaluated group with good to excellent results, with few radiographic failures, acceptable implant survival at 2 years comparable with the control and that in the conventional hip implant literature, and improved physical quality of life scores on the SF-12 health survey. Range of motion improved in both groups as compared to preoperative measurements, but was not statistically significant. Overall success rates are no worse than the control. The patient pain and function outcomes are comparable to the control and similar to what is expected from similar devices in a historical perspective.

Overall Conclusions

The pre-clinical and clinical data demonstrate that the Reflection Ceramic Acetabular System trial has met their objective and have provides reasonable assurance that the Reflection Ceramic Acetabular System is safe and effective when used as directed for total hip arthroplasty in patients requiring primary total hip arthroplasty due to non-

inflammatory arthritis (degenerative joint disease) such as osteoarthritis, avascular necrosis, or traumatic arthritis. Analysis has demonstrated that the Reflection Ceramic Acetabular System met the statistical noninferiority endpoint study goal when used as intended in the non-inflammatory arthritis indication as compared to the control.

XII. PANEL RECOMMENDATIONS

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA application was not referred to the Orthopedic Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

The applicant has adequately submitted all answers to the FDA's previous questions and comments for their Premarket Approval application. Therefore, the preclinical and clinical data provides reasonable assurance that the Reflection Ceramic Acetabular System is safe and effective when used as directed for total hip arthroplasty in patients requiring primary total hip arthroplasty due to non-inflammatory arthritis (degenerative joint disease) such as osteoarthritis, avascular necrosis, or traumatic arthritis.

In addition, the applicant has agreed to conduct a post approval study to further evaluate the long-term safety and effectiveness of the device. Follow-up of patients will be requested from all ten original investigational sites. Full clinical and radiographic data in accordance with the PMA post approval study protocol will be collected for both the study (C/C) and control (C/P) groups. All RNIA and RIA cohort patients will be followed annually through five (5) years postoperative until the required population is achieved and reported annually until all patients have reached their 5 year post-operative time point. Additionally, the Continued Access (CAC) patients enrolled at applicable sites will be followed annually through two (2) years and reported annually. Some CAC cohort patients may be followed to five years as necessary to reach the minimum study sample size of 100 patients at the end of 5 years. In this case, these CAC patients will be reported annually until patients have reached their 5 year post-operative time point. In addition, an explant analysis of any Reflection component that is implanted and subsequently removed will be collected as specified in the Post approval study protocol and included in annual reports. All patients enrolled in the original study cohorts (i.e. from all 10 sites) as well as the CAC patients will be sent a letter questionnaire annually at the 6-10 year post-operative time points to assess the patient's general well-being and if the study components are still in place.

The questions will consist of the following:

"Has your hip prosthesis been revised or replaced?" (Yes or No)

"Are you satisfied with how your hip prosthesis is functioning?" (Yes or No)

"Do you expect to have your hip prosthesis removed in the near future?" (Yes or No)

Therefore, since all the conditions of approval have been met, FDA finds in favor of approval of the Reflection[®] Ceramic Acetabular System.

FDA issued an approval order on December 17, 2004.

The applicant's manufacturing facilities were inspected and were found to be in compliance with the Quality System Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings and Precautions, and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.